

**REMARKS****Claim Amendments**

Claims 1-4 and 19-22 have been amended. Claim 27 has been added. Following this Amendment, claims 1-17 and 18-27 will be pending. Of these, claims 5-17 have been withdrawn from consideration.

Claims 1 and 2 have been amended to remove the recitation of "*ptc* therapeutic," in order to further clarify the claimed subject matter; claims 19-22 have been similarly amended. Claims 1 and 2 have also been amended to recite "hedgehog signaling" instead of "hedgehog/patched signal transduction." Support can be found, for example, at page 53, lines 14-17; page 68, lines 28-29; page 70, lines 26-29; page 71, lines 17-18; page 72, lines 17-18; and page 73, lines 1-4 of the specification.

Claims 3 and 4 have been amended to have antecedent basis in claim 1 and to remove the recitation of how the agent is provided or administered. The dependency of claim 21 has been amended.

No new matter has been added.

**Withdrawn Objections and Rejections**

Applicants acknowledge with appreciation the withdrawal of the objections to and/or rejections of claims 1-4, 19-23, 25 and 26, and the partial withdrawal of the rejection of claims 2 and 19-24.

**Objection to Claim 21**

Claim 21 is objected to for being of improper dependent form for failing to further limit the subject matter of a previous claim. Claim 21 has been amended to depend only from claim 20, so that claim 21 now limits the subject matter of the claim from which it depends. Withdrawal of the objection is respectfully requested.

Rejection of Claims 2 and 19-24 Under 35 U.S.C. § 112, First Paragraph (Enablement)

Claims 2 and 19-24 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. Applicants respectfully traverse the rejection. Applicants note with appreciation that the Examiner has recognized that a claim to contacting embryonic lung tissue from a *Shh* mutant mouse is enabled.

The Examiner has failed to give appropriate weight to the recited step of "whether the agent induces the formation of, or the maintenance or functional performance of normal lung tissue" in the enablement analysis. On the top of page 7, the Examiner states that "the skilled artisan at the time of filing of the instant application could not predict whether or not a compound that promotes patched signal transduction could also induce normal lung tissue." Because of the recited step listed above, it is immaterial whether a skilled artisan could predict the behavior of a compound. The claimed method would only identify those compounds that **both** promote signal transduction and induce formation of or maintenance of functional performance of normal lung tissue, so that there are no inoperative embodiments. No prediction of an end result is required.

With respect to testing on cancer cells and other transgenic animals, Applicants again note that claims 2 and 19-24 all require that "the agent induces the formation of, or the maintenance or functional performance of normal lung tissue" before an agent is identified by the claimed method. Thus, the claimed method requires that there be a correlation between mechanism and biological activity before an agent is identified. Again, there are no inoperative embodiments in the claimed method; the Examiner is cautioned against equating a negative result from the claimed method with an inoperative embodiment.

The Examiner also appears to suggest that the claims require one to prepare "any and all transgenic non-human animals." A similar argument is made for embryonal cells (e.g., embryonic stem cells). The Examiner's reasoning is not understood. The claimed method provides a general way of screening agents for the recited activities. Applicants are not claiming the preparation of new transgenic animals and embryonal cells. While such animals and cells

could certainly be used in the claimed method, it is simply unreasonable to require Applicants to teach how to prepare every possible organism, tissue or cell type that could be used in the claimed method. Applicants are aware of no legal basis for such a requirement, because *nearly any screening method would be rejected on a basis that has little to do with the screening method itself*. This aspect of the rejection is illogical.

Thus, when proper weight is given to *all* steps of claims 2 and 19-24, the claims are fully enabled. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-4, 19-21, 25 and 26 Under 35 U.S.C. § 112, First Paragraph (Written Description)

Claims 1-4, 19-21, 25 and 26 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants respectfully traverse the rejection, to the extent that it applies to the claims as amended.

The Examiner states that the specification does not describe examples of *ptc* therapeutics other than inhibitors of protein kinase A, hedgehog proteins and/or antisense constructs. As discussed above, the independent claims have been amended to be directed to methods for screening for "agents". An "agent" can be any compound contemplated by the specification. As this is a *screening method*, no guidance on the individual agents to be tested should be required, although several of the dependent claims enumerate types of agents that can be screened according to the claimed method or additional activities that an agent may have. For this reason, the bases for the rejection are no longer applicable to the claims as amended. Applicants note, however, that agents identified by the claimed methods would generally be termed *ptc* therapeutics. Reconsideration and withdrawal of the rejection are requested.

Rejection of Claim 1-4 and 19-26 Under 35 U.S.C. § 112, Second Paragraph

Claims 1-4 and 19-26 is rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner states that claim 1 is indefinite because it recites "wherein the agent is a *ptc* therapeutic" and it is allegedly unclear whether the claimed method is limited to screening agents that are previously known as *ptc* therapeutics. As discussed above, the method identifies new *ptc* therapeutics. In order to further clarify the claimed subject matter, the claims have been amended to delete this recitation.

The Examiner also state that claim 1 is indefinite for reciting "hedgehog/patched signal transduction" because the term is not defined in the specification. Claims 1 and 2 have been amended to recite "hedgehog signaling". The term hedgehog signaling was, at the time of filing, and still is used throughout the scientific literature to refer to the signaling cascade normally mediated by hedgehog and patched protein. Additionally, the term is similarly used in Applicants' specification, for example, at page 53, lines 14-17; page 68, lines 28-29; page 70, lines 26-29; page 71, lines 17-18; page 72, lines 17-18; and page 73, lines 1-4.

Claims 3 and 4 have been rejected for a number of antecedent basis issues. The claims have been amended to address these issues.

Withdrawal of the rejection is respectfully requested.

Rejection of Claims 1, 3, 4, 21, 25 and 26 Under 35 U.S.C. § 103(a)

Claims 1, 3, 4, 21, 25 and 26 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Marigo *et al.* (US 6,261,786) and Fujita *et al.* (BBRC 238: 658-665, 1997). The Examiner states that "[i]t would have been obvious to the person of ordinary skill in the art at the time the invention was made to perform a method of screening comprising contacting a cell culture of the LK-2 lung cancer cells taught by Fujita with a small organic molecule as taught by Marigo and measure hedgehog signaling pathway (by measuring patched gene expression) as taught by Marigo and growth as taught by Fujita." Applicants respectfully traverse the rejection.

The teachings of Fujita *et al.* are limited to antibodies inhibiting the growth of LK-2 cells. Fujita *et al.* do not teach or otherwise suggest that small molecules would be useful in inhibiting the growth of lung cancer cells. Because of this, one of ordinary skill in the art would have had no reasonable expectation of success that the claimed method would be successful. Absent the

reasonable expectation of success, the claimed method cannot be obvious in view of the cited references. Reconsideration and withdrawal of the rejection are respectfully requested.

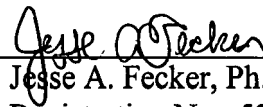
Applicants note that new claim 47 is nonobvious over Marigo *et al.* and Fujita *et al.*, at least because neither reference, separately or in combination, teaches or otherwise suggests a method of screening for an agent for inhibiting or reducing the proliferation or growth of cells, comprising contacting *normal lung cells* with an amount of an agent.

### CONCLUSION

If any clarification of the above response would facilitate prosecution of this application, Applicants respectfully request that the Examiner contact the undersigned at 617-951-7000. Any fee required for timely consideration of this submission may be charged to **Deposit Account No. 18-1945, under Order No. HUIP-P02-032.**

Respectfully Submitted,

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